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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/411,006	10/01/1999	ROSS WALDEN TYE	07207.0002US	7762

22930 7590 05/20/2003

HOWREY SIMON ARNOLD & WHITE LLP
BOX 34
1299 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

EXAMINER

GUPTA, ANISH

ART UNIT	PAPER NUMBER
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1654

DATE MAILED: 05/20/2003

11

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/511,006

Applicant(s)

HENEGAR ET AL.

Examiner

Anish Gupta

Art Unit

1654

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 July 2001.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-64 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-64 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____

- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

Election/Restriction

1. Applicant's election without traverse of Group I in Paper No. 7 is acknowledged. Claims 1-64 have been examined in this application and an office action follows below.

All rejection made in the previous office action and not cited herein are withdrawn. New Grounds for Rejections follow below.

New Grounds For Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

2. Claims 1-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tye in view of Bucci et al. and Rauch et al.

The claims are drawn to a non pyrogenic, endotoxin free, oxygen free, stroma free, cross-linked hemoglobin, cross linked with bis dibromo salicyl fumarate and modified by pyridoxal-5'-phosphate.

The reference of Tye et al. teach a stroma free tense state tetrameric hemoglobin cross linked with bis(3,5-dibromosalicyl)-fumarate and modified with pyridoxal-5'-phosphate (see claim 1 and 3 of the patent). The modified hemoglobin serves as a blood substitute product with a storage life of greater than two years (see col. 6, lines 50-64). Further, the modified hemoglobin has

“superior oxygen transport capabilities not found in stroma free hemoglobin” (see col. 7, lines 5-11). The method of making the modified hemoglobin involves the isolation of hemoglobin, subjecting the solution to a vacuum and flushing with inert gas until the oxygen tension is decreased at a value of 1.0mm Hg, reacting with bis(3,5-dibromosalicyl)-fumarate (BDBF), finally modifying with pyridoxal-5'-phosphate (see col. 9, lines 39-68 and col. 10, lines 1-36). The source of the hemoglobin can include human, bovine, bovine, or porcine (see col. 8, lines 17-20). The difference between the prior art and the instant application is that the reference does not teach removing endotoxin from preparation containing red blood cells, removing oxygen from red blood cells, and lysing red blood cells.

However, Bucci et al. states that it is necessary to have the hemoglobin in deoxy form for the pyridoxylation with pyridoxal-5'-phosphate (see col. 3, lines 58-62). The reference teach various methods for deoxygenation hemoglobin prior to pyridoxylation. One method involves the suspension of red blood cells with a reducing agent to maintain the solution in deoxy form (see col. 3, lines 50-64). The solution with the red blood cells are then subjected to a heating step that lyses the cells and extracts the free reduced hemoglobin (see col. 3, lines 65-68). Before the polymerization, the solution is subject to precipitation and centrifugation to remove all of the organic and inorganic material from hemoglobin (see col. 5, lines 57-64). The reference further states that the reducing agent maintains the environment oxygen free. Moreover, although not necessary, an atmosphere of an inert, oxygen free gas may be present, such as nitrogen or argon. The reference states, however, the “necessary reaction condition in this respect maintaining an oxygen free atmosphere] can easily be determined by a person skilled in the art” (see col. 4, lines 53-68 and col. 5, lines 39-44). Note that Tye teach that the environment can be maintained oxygen

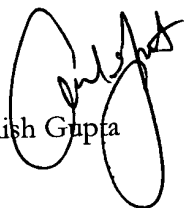
free by purging the environment with an inert gas and removing the gas by vacuum (see Tye col. 10, lines 3-5). Finally, Bucci et al. teach that the starting material can also be blood cells which have been subject to lysis and from which the stroma has been removed completely or partially (see col. 3, lines 43-46).


Rausch et al. acknowledges that Tye et al. Does not teach that the hemoglobin preparation is endotoxin free (see col. 5, lines 60-66). The reference states that endotoxin causes fever, diarrhea, hemorrhagic shock, and other tissue damages (see col. 12, lines 32-37). Therefore, a low concentration of endotoxin is desired. Rauch also discloses that the hemoglobin can be crosslinked after removal of endotoxin and red-blood cell clarification (see col. 12, lines 67-68). The reference also teach that the product obtained has a phospholipid concentration of less than about 1 nanogram per mL (see claim 9). Further, during the ultrafiltration stage, a process used to remove endotoxin, pyrogen are also removed since pyrogen are between 100,000 and 1 million in molecular weight (see col. 17, lines 46-55). Thus, the reference discloses that when endotoxin free hemoglobin is obtained, the process yields a pyrogen free product as well. Therefore, in order to achieve a endotoxin concentration of .5EU/mL, it would have been obvious to optimize the initial cell separation, as disclosed by Rausch, to avoid complications such as caus fever, diarrhea, hemorrhagic shock, and other tissue damage that are associated with endotoxin. It would have been further obvious to one of ordinary skill in the art to utilize the method disclosed in Bucci et al. to maintain the hemoglobin in deoxygenated from because deoxy-hemoglobin is necessary for polymerization to occur.

3. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anish Gupta whose telephone number is (703) 308-4001. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, can normally be reached on (703)306-3220. The fax phone number of this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Anish Gupta




BRENDA BRUMBACK
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600